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Association between cognitive performance, physical fitness, and physical activity level in women with chronic fatigue syndrome

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Abstract—Limited scientific evidence suggests that physical activity is directly related to cognitive performance in patients with chronic fatigue syndrome (CFS). To date, no other study has examined the direct relationship between cognitive performance and physical fitness in these patients. This study examined whether cognitive performance and physical fitness are associated in female patients with CFS and investigated the association between cognitive performance and physical activity level (PAL) in the same study sample. We hypothesized that patients who performed better on cognitive tasks would show increased PALs and better performance on physical tests. The study included 31 women with CFS and 13 healthy inactive women. Participants first completed three cognitive tests. Afterward, they undertook a test to determine their maximal handgrip strength, performed a bicycle ergometer test, and were provided with an activity monitor. In patients with CFS, lower peak oxygen uptake and peak heart rate were associated with slower psychomotor speed ($p < 0.05$). Maximal handgrip strength was correlated with working memory performance ($p < 0.05$). Both choice and simple reaction time were lower in patients with CFS relative to healthy controls ($p < 0.05$ and $p < 0.001$, respectively). In conclusion, physical fitness, but not PAL, is associated with cognitive performance in female patients with CFS.

Key words: aerobic capacity, chronic fatigue syndrome, cognitive functioning, maximal handgrip strength, physical activity, physical fitness, psychomotor speed, reaction time, vigilance, working memory.

Abbreviations: ANOVA = analysis of variance, CDC = U.S. Centers for Disease Control and Prevention, CFS = chronic fatigue syndrome, HR = heart rate, HR_p = peak heart rate, HR_{rest} = resting heart rate, MET = metabolic equivalent, OSPAN = operation span task, PAL = physical activity level, PVT = psychomotor vigilance task, RER_p = peak respiratory exchange ratio, SD = standard deviation, SWA = SenseWear® Pro3 Armband, VO_{2p} = peak oxygen uptake.

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INTRODUCTION

Chronic fatigue syndrome (CFS) is defined by the U.S. Centers for Disease Control and Prevention (CDC) as a condition characterized by self-reported unexplained persistent or relapsing fatigue of at least 6 mo duration and the concurrent occurrence of multiple nonspecific symptoms, including sore throat, muscle and joint pain, headache, tender cervical or axillary lymph nodes, unrefreshing sleep, and postexertional malaise [1].

Cognitive complaints are some of the most frequent and significant contributors to social and occupational dysfunction in people with CFS [2]. These complaints are particularly mentioned in the form of memory and concentration problems [3–4]. Some studies, in which objective measures were used to evaluate cognitive performance, have reported slowed psychomotor and/or processing speed [5–10], impaired working memory [6–8,11–12], and poor information learning [3,8,13–15] in patients with CFS, while others found no abnormalities in these domains (psychomotor and/or processing speed [11,16–17], working memory [3,18], and information learning [16,19]). Differences in testing batteries, diagnostic heterogeneity, comorbid psychiatric disorders, and medication usage could be the cause of these inconsistent findings.

Besides the frequently reported cognitive complaints in people with CFS, daily physical activity level (PAL), measured by accelerometry (counts/time), is also significantly reduced relative to healthy controls. PAL refers to the amount of physical activity performed during daily life. This was confirmed by the results of two systematic literature reviews [20–21]. In both reviews [20–21], all the included studies on PAL in patients with CFS (n = 5 in both reviews) used real-time accelerometry and found significantly lower PALs among patients with CFS than in healthy controls. Furthermore, PALs in people with CFS seem to correlate with symptom severity and variability [22]. In their discussion paper, Wessely et al. suggested that persistent inactivity caused by symptoms like pain and fatigue leads to deterioration of physiological exercise capacity and the subsequent presence of more symptoms, which eventually results in a vicious and self-perpetuating cycle of activity avoidance [23]. This avoidance behavior toward physical activity is in turn likely to influence PAL and exercise performance. A logical consequence would be that the exercise capacity in patients with CFS is significantly lower than in healthy controls. However, a systematic literature review recently conducted by Nijs et al. revealed no definite conclusion in relation to physiological exercise capacity in patients with CFS [20]. Sources of bias such as the lack of uniformity in sex, exercise testing protocols, PAL, and utilized diagnostic criteria for CFS might be explanatory factors for these conflicting findings.

In previous work, a significant positive correlation was found between cognitive dysfunction and low PALs [24] and cognitive impairment and the degree of functional impairment among patients with CFS [25]. These findings suggest that physical activity is directly related to cognitive performance in patients with CFS. Yet to date, no study has examined the direct relationship between cognitive performance and physical fitness (and physiological exercise capacity in particular) in people with CFS.

First, this study aimed at examining the relation between cognitive performance and physical fitness in female patients with CFS. Likewise, the relation between cognitive performance and PAL was examined. We hypothesized that patients who performed better on cognitive tasks would show increased PALs and better performance on physical tests.

Second, given the inconsistencies in available data both in terms of objective cognitive findings and physiological exercise capacity findings in CFS, this study examined cognitive performance and physical fitness in female patients with CFS. For this purpose, we excluded patients experiencing major depression with psychotic or melancholic features and/or other psychiatric disorders that can explain the presence of chronic fatigue from study participation. Furthermore, we compared the results of patients with CFS with those of an inactive sex-, age-, height-, and body mass-matched healthy control group.

METHODS

Study Design

The study was designed as a prospective case-controlled comparison and took place at a private practice for internal medicine in Ghent (Belgium).

Participants

Patients with CFS were recruited via a private practice for internal medicine. To be included in the study, they had to comply with the 1994 CDC criteria for CFS [1]. The same internal medicine physician diagnosed all patients. Other inclusion criteria included being female, because pooling of sex data has been identified as an important source of bias in addressing exercise physiology in patients with CFS [26], and between 18 and 45 yr old. Based on the results of a previous study on cognitive performance in patients with CFS, the power analysis revealed that a sample size of 31 patients with CFS would provide an 80 percent power and alpha of 0.05 [8].

We asked all of the included patients with CFS to bring a healthy (pain-free and without any [chronic] disease) and inactive relative, friend, or acquaintance to participate in the control group. We defined inactive as having a seated occupation and performing a maximum of 1 h of exercise per week [27]. Controls had to meet the same additional inclusion criteria (sex and age) as the patients with CFS. Exclusion criteria for both the patients with CFS and controls included pregnancy and the presence of intellectual disabilities. The internal medicine physician carefully selected the patients with CFS and thereby excluded all women who were pregnant. This was asked in advance of both the patients and controls. In any case of doubt, a pregnancy test was used. To determine the presence of intellectual disabilities, we relied on the medical records of the patients with CFS. If the diagnosis was not mentioned in the medical record, we assumed that no intellectual disability was present. The controls had to be pain-free and could not suffer from any (chronic) disease. This was always asked in advance, and when the presence of a disease was suspected, the general practitioner could always be contacted. This was never necessary. Furthermore, on the testing day, we asked every participant to refrain from using substances like caffeine, alcohol, and nicotine, which could influence physical and/or cognitive performance. We excluded participants who used drugs known to influence cognitive function (opioids, antidepressants, anticonvulsants, benzodiazepines).

Procedure

Potential study participants were first informed about the study by their physician, then asked to read an information leaflet. Next, written informed consent was obtained from all participants. After we collected information on personal characteristics and measured participants' weight and height, we asked them to complete three cognitive tests. To examine physical fitness, all participants completed a test to determine their maximal handgrip strength, performed an exercise test on a bicycle ergometer with continuous cardiorespiratory monitoring (ergospirometry), and were provided with an activity monitor to register daily physical activity during 72 consecutive hours. **Figure 1** shows the flowchart of the study.

Cognitive Tests

To investigate cognitive function, we used the Stroop task, the psychomotor vigilance task (PVT), and the operation span task (OSPAN) with concomitant mathematical processing to assess selective attention and choice reaction time, vigilance and alertness, and working memory capacity, respectively. All three tests were conducted on the same computer and in the same order (Stroop task, PVT, OSPAN) by every participant. To ensure standardization of the procedure, each test began with the presentation of written instructions for that particular test. Short breaks (±5 min) between each test were allowed.

In the Stroop task [28] examining cognitive control, all the possible interference effects inherent to the Stroop paradigm were examined (semantic, emotional, and priming). In this task, responses were collected through the computer keyboard. Different words were presented one by one and in various font colors (yellow, green, red, and blue) in the middle of the screen on a white background. Participants were instructed to respond to the presented font color in which words were written by pressing the corresponding colored key as quickly and as accurately as possible. The computer stored response times and accuracy. The task began with a practice block,

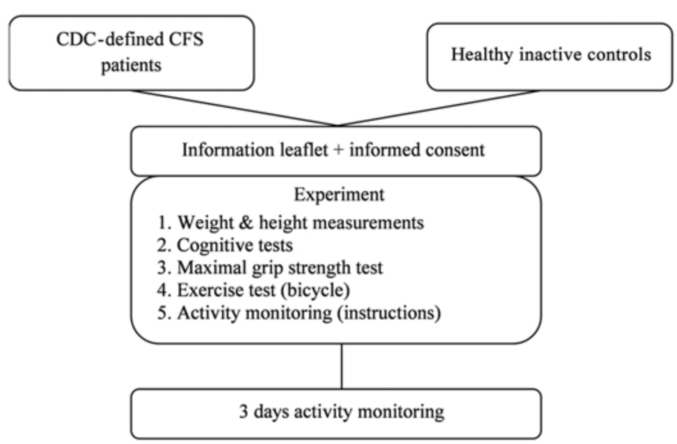

Figure 1.
Flowchart of study. CDC = U.S. Centers for Disease Control and Prevention, CFS = chronic fatigue syndrome.

during which participants received feedback about their performance ("correct" or "incorrect" and response time). The presented words/nouns could be classified under eight different conditions, namely category (animal names written in one color), congruent (same word and color, e.g., the word "red" displayed in red font), incongruent (different word and color, e.g., the word "red" displayed in green font), neutral (neutral words written in one color, e.g., "windowsill," "plate," "circus"), no word ("XXX" presented in one color), priming negative inverse (e.g., the word "red" displayed in green font immediately followed by the word "green" displayed in red font), priming negative simple (e.g., the word "red" displayed in green font immediately followed by the word "blue" displayed in red font), and sleep (sleep-related words written in one color, e.g., "nap," "night[time]," "fatigue," "blanket").

In the PVT [29], which is a test of simple reaction time, participants responded to a visual stimulus that appeared on the screen (always in the middle) at random interstimulus intervals (2–10 s). The written instructions told them to take the mouse in their dominant hand, not to support their arm, and to press either the left (for left-handed people) or the right (for right-handed people) mouse button with the thumb as quickly as possible whenever they perceived the appearance of the stimulus (a fireball) on the screen. Participant's reaction time was displayed on the screen for 1 s. If the participant did not respond within 500 ms, the trial was stored as a lapse and a warning message appeared. The PVT test duration was 10 min.

Like the PVT, the OSPAN (based on Conway and Engle [30]) was completely mouse-driven. The task began with a practice block (divided into three sections). First, participants practiced the simple letter span in which they saw letters appear on the screen one at a time and had to recall these letters in the same order they saw them. The second practice was the math portion of the OSPAN. First, a math operation appeared on the screen (e.g., (7 × 3) – 3 = ?). Next, a number (e.g., 18) was presented and participants were instructed to click if the number was the correct solution by clicking on "true" or "false." After the recall of each letter span and after each math operation, participants were given feedback about their performance. To account for individual differences, the program calculated how long it took a given participant to solve each of the math problems. The average time plus 2.5 standard deviation (SD) was then used in the experimental block as a time limit to solve the operations, thus preventing participants from rehearsing the letters when they should be solving the operations. The final practice session consisted of exercises as they would appear during the experimental block, meaning that both the letter recall and the math operations had to be performed together. Participants first had to solve the math operation and only then saw the letter to be recalled. After the completion of all practice sessions, the program automatically proceeded to the experimental block, which consisted of three sets of each set size (ranging from 3 to 7). Thus, a total of 75 letters and 75 math problems were presented. During letter recall, a math accuracy percentage was presented in the upper right-hand corner. Participants were instructed to keep their math accuracy at or above 85 percent at all times. At the end of the OSPAN experiment, five values were registered, namely score (sum of the letters in all perfectly recalled letter sets), total (sum of letters recalled in the correct position, regardless of whether the set was correct), accuracy error (number of wrong answered math operations), speed error (number of answers beyond the allowed time), and math error (sum of accuracy error and speed error).

Maximal Handgrip Strength Test

We measured maximal handgrip strength using a hydraulic hand dynamometer (Jamar dynamometer, Saehan Corporation; Masan, Japan) with an adjustable handle and an analogous reproduction of the delivered power in kilogram-force and pound-force. Participants sat on a chair while holding the dynamometer in their dominant hand with the elbow flexed at 90° and the forearm in neutral position. The analog screen was turned away from the participants so they could not read the amount of generated force. They were then instructed to grip the instrument as hard as possible in three consecutive attempts. The highest score was recorded. Data from a study by Peolsson et al. demonstrated excellent inter- and intrarater reliability for the Jamar dynamometer with intraclass correlation coefficients ranging from 0.94 to 0.98 [31]. This type of hydraulic hand dynamometer also showed good concurrent validity (r = 0.9998) with known weights [32].

Exercise Test

Participants performed the exercise test on a computer-controlled cycle ergometer (eBike Comfort, GE

Healthcare; Freiburg, Germany). They were first given 3 to 5 min to adjust to the test position, after which we collected baseline data. Pulmonary data (peak oxygen uptake [VO_{2p}] and peak respiratory exchange ratio [RER_p]) were acquired breath-by-breath using a computerized Vmax–229 series spirometer (SensorMedics; Yorba Linda, California). Heart rate (HR) was calculated using an electrocardiograph (Cardiosoft™, GE Healthcare). The test started at a workload of 60 W, which was increased by 30 W every minute. Participants pedaled at a speed of 60 to 70 rotations per minute. The exercise test was finished when they were exhausted and, consequently, their pedaling rate sank below 55 rotations per minute. Cool-down included 1 min of cycling at a rate of 20 rotations per minute and a workload of 30 W.

Real-time Activity Monitoring

We used the SenseWear® Pro3 Armband (SWA) (BodyMedia Inc; Pittsburgh, Pennsylvania) wireless multisensor accelerometer for real-time monitoring of physical activity of all participants during 3 consecutive days. This activity monitor has a two-axis accelerometer, along with several other physiological sensors (heat flux, skin temperature, near-body ambient temperature, body position, movements of the upper arm, and galvanic skin response) from which data are integrated and can subsequently be uploaded and analyzed using computer software. Energy expenditure, which we calculated at 1 min intervals for this study, is estimated based on sex, age, height, and weight, together with the information collected from all sensors. The SWA also registered the time when energy expenditure was >3 metabolic equivalents (METs), the time spent sleeping, and the time spent awake in supine position. The SWA is lightweight and comfortable to wear, worn on the back of the right upper arm over the triceps muscle. Good validity and reliability of the SWA has been shown in healthy adults under laboratory [33] and free-living conditions [34].

Statistical Analysis

We performed data analyses using SPSS version 19.0 for Windows (IBM Corporation; Armonk, New York). All data subsets were assessed for normal distribution using the Kolmogorov-Smirnov goodness of fit test and appropriate descriptive statistics were calculated. For normally distributed data subsets, parametric statistics were used (Student *t*-test, Pearson correlations). Subsets that were not normally distributed were analyzed with nonparametric tests (Mann-Whitney *U* test, Spearman correlations). Stroop interference, priming, and emotional effects were investigated separately using a 3 × 2 analysis of variance (ANOVA), with Stroop condition as within-subject factor and group as between-subject factor. To investigate the Stroop interference effect, we performed the ANOVA on the mean reaction times of the congruent, incongruent, and no word conditions. Mean reaction times of incongruent, negative priming inverse, and negative priming simple stimuli were analyzed together in order to determine possible priming effects. The presence of emotional Stroop effects was investigated by performing an ANOVA on the mean reaction times of three conditions comprising nouns with different levels of emotional load, namely animal names (category condition), neutral words, and sleep-related words. After an arcsine transformation, Stroop accuracy data were also submitted to a 3 × 2 ANOVA and further analyzed in the same way as the Stroop reaction time data. The significance level for all statistical tests was set a priori at $p < 0.05$.

RESULTS

We recruited 31 women with CFS. From all of the controls who agreed to study participation, we were able to recruit and match 13 with patients with CFS. The controls consisted of healthy women matched for age, height, body mass, and body mass index, as shown in **Table 1**. All participants had the same ethnic background (native Dutch-speaking women from Flanders). Because of missing data due to dropout (of the patients with CFS, 1 refused to perform the exercise and maximal handgrip strength test because she felt nauseous and 6 did not wear the SWA properly), data loss (1 participant in both groups for the maximal handgrip strength test), technical problems with the test computer (1 patient with CFS and 2 controls for the PVT and OSPAN and 1 control for the Stroop task), and technical problems with the SWA (3 patients with CFS), the number of data analyzed for each test in each group does not always equal the total number of recruited participants.

Cognitive Performance: Group with Chronic Fatigue Syndrome Versus Healthy Inactive Control Group

Stroop Task

The 3 × 2 ANOVA on Stroop reaction times of the congruent, incongruent, and no word conditions exhibited a significant main effect of condition ($F(2,82) = 6.31$, $p <$

Table 1.
Baseline characteristics of patients with chronic fatigue syndrome (CFS) and healthy inactive control participants. Data presented as mean ± standard deviation.

Characteristic	CFS (n = 31)	Control (n = 13)	p-Value*
Age (yr)	35.6 ± 7.6	29.0 ± 12.0	0.12
Body Mass (kg)	64.9 ± 10.8	64.6 ± 9.5	0.93
Height (cm)	166.5 ± 5.1	168.4 ± 6.9	0.36
Body Mass Index	23.4 ± 3.7	22.8 ± 3.7	0.68

*Comparisons performed using Student *t*-test.

0.01) and group ($F(1,41) = 7.11$, $p = 0,01$) but no interaction between both ($F(2,82) = 1.44$, $p > 0.1$). Subsequent post hoc analysis (Bonferroni correction) revealed that the differences between reaction times on the incongruent and congruent conditions as well as between the incongruent and no word conditions were significant ($p < 0.05$ and $p = 0.01$, respectively) (**Figure 2(a)**).

For reaction times of incongruent, negative priming inverse, and negative priming simple stimuli, the ANOVA showed a significant main group effect ($F(1,41) = 6.26$, $p < 0.05$). There was no effect of condition ($F(2,82) = 1.01$, $p > 0.1$) and no interaction between group and condition ($F(2,82) = 1.95$, $p > 0.1$) (**Figure 2(b)**).

Figure 2(c) depicts the significant difference in reaction times between the CFS and control groups for words with different levels of emotional load (main effect of group) ($F(1,41) = 7.23$, $p = 0.01$). No significant effect of condition ($F(2,82) = 0.51$, $p > 0.1$) or interaction between group and condition ($F(2,82) = 0.35$, $p > 0.1$) was found.

For Stroop accuracy of the congruent, incongruent, and no word conditions, a 3 × 2 ANOVA showed a marginally significant main effect of condition ($F(2,82) = 3.1$, $p = 0.05$) but no effect of group ($F(1,41) = 2.76$, $p > 0.1$) and no interaction between group and condition ($F(2,82) = 1.55$, $p > 0.1$). The post hoc analysis for condition revealed marginally significant differences between accuracy scores of the congruent and incongruent conditions ($p = 0.05$) (**Figure 2(d)**).

No effect of group ($F(1,41) = 0.01$, $p > 0.1$), condition ($F(2,82) = 1.33$, $p > 0.1$), or interaction ($F(2,82) = 0.2$, $p > 0.1$) was found for accuracy scores in priming tasks (incongruent, negative priming inverse, and negative priming simple) (**Figure 2(e)**).

Figure 2(f) depicts a significant main effect of group ($F(2,82) = 3.2$, $p < 0.05$) and condition ($F(1,41) = 4.15$, $p < 0.05$) and an interaction effect between both ($F(2,82) = 5.75$, $p < 0.01$) for Stroop accuracy scores in words with different levels of emotional load. The post hoc analysis for condition revealed a marginally significant difference ($p = 0.05$) between Stroop accuracy for animal names (category condition) and sleep-related words in the control group. Because we wanted to investigate whether the main effect of group was not only the result of the large visible difference (**Figure 2(f)**) in accuracy for sleep-related words, we submitted the accuracy data of all three conditions to a Mann-Whitney *U* test. The analyses revealed a significant difference between Stroop sleep condition accuracy scores ($p = 0.01$), with superior scores in the CFS group. No differences were found in Stroop category and neutral condition accuracy (both $p > 0.1$).

Psychomotor Vigilance Task and Operation Span Task

Table 2 presents the mean scores of both groups on the PVT and OSPAN. Patients with CFS showed a significantly higher percentage of lapses on the PVT (mean ± SD: 30.6% ± 36.6%) than controls (2.8% ± 1.9%) ($p < 0.001$). No significant differences were found in any of the five OSPAN scores ($p > 0.05$).

Physical Fitness: Group with Chronic Fatigue Syndrome Versus Healthy Inactive Control Group

Data acquired during the bicycle ergometer exercise test revealed that patients with CFS achieved a significantly lower workload at peak effort and had a lower peak HR (HR_p) and VO_{2p} ($p < 0.001$) than controls. Resting HR (HR_{rest}), RER_p, and maximal handgrip strength were not found to be different between groups ($p > 0.05$) (**Table 3**).

Relationship Between Cognitive Performance and Physical Fitness in Patients with Chronic Fatigue Syndrome

VO_{2p} was inversely related to all components of Stroop reaction time as well as to PVT reaction time ($p < 0.05$). The analyses also yielded significant negative correlations between five out of eight Stroop reaction time parameters and HR_p and between reaction time

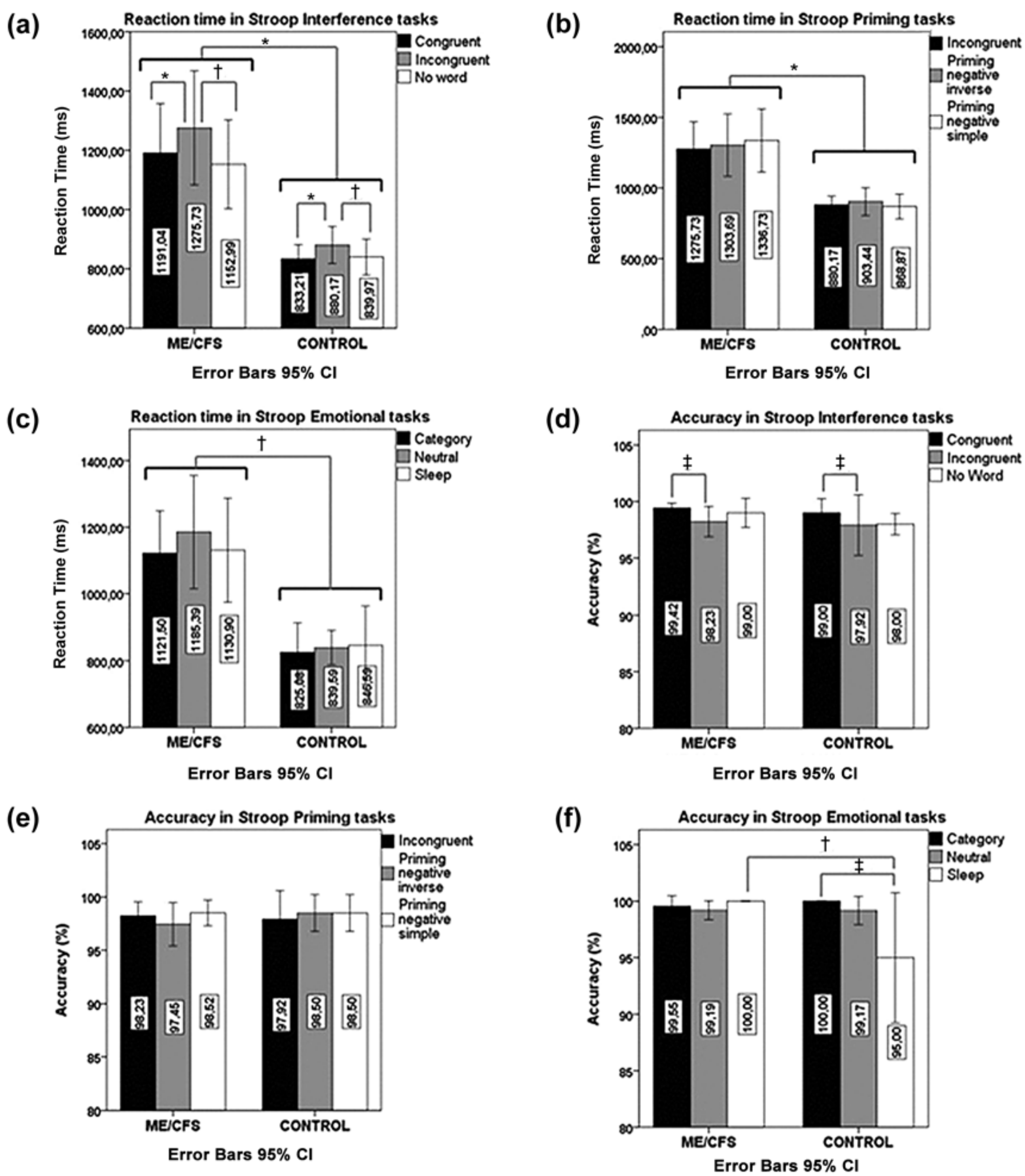

Figure 2.
Stroop task performance. (**a**) Difference in reaction times between patients with chronic fatigue syndrome (CFS) and healthy inactive control participants in congruent, incongruent, and no word conditions, and difference in reaction times in incongruent and congruent and in incongruent and no word conditions in both patients with CFS and controls indicating Stroop interference effect of same magnitude. Difference in reaction times between patients with CFS and controls in (**b**) priming tasks and (**c**) nouns with different levels of emotional load (category, neutral, and sleep conditions). (**d**) Difference in accuracy between congruent and incongruent conditions in both patients with CFS and controls. (**e**) Comparisons between incongruent, priming negative inverse, and priming negative simple conditions for accuracy. (**f**) Difference in accuracy between patients with CFS and controls for sleep-related words, and difference in accuracy between category and sleep stimuli in controls. All comparisons were performed using 3 × 2 analysis of variance with condition as within-subject factor and group as between-subject factor. Additional analyses between accuracy scores of both groups in nouns with different levels of emotional load (category, neutral, and sleep conditions) were conducted using Mann-Whitney *U* test. Error bars indicate standard error. Marginally statistically significant effects: $^{*}p < 0.05$, $^{\dagger}p \leq 0.01$, $^{\ddagger}p = 0.05$. CI = confidence interval, ME = myalgic encephalomyelitis.

Table 2.
Comparison of psychomotor vigilance task (PVT) and operation span task (OSPAN) scores between patients with chronic fatigue syndrome (CFS) and healthy inactive control participants. Data presented as mean ± standard deviation. Statistically significant results are bold.

Variable	CFS (*n* = 30)	Control (*n* = 11)	*p*-Value
PVT			
Reaction Time (ms)	357.6 ± 45.4	289.1 ± 23.5	**<0.001***[*]
Lapses (%)	30.6 ± 36.6	2.8 ± 1.9	**<0.001**[†]
OSPAN			
Math Error	7.3 ± 3.3	6.5 ± 5.4	0.56[*]
Accuracy Error	5.8 ± 3.0	3.7 ± 2.4	0.05[*]
Speed Error	1.5 ± 2.0	2.7 ± 5.2	0.54[†]
Score	27.8 ± 19.5	34.7 ± 18.3	0.31[*]
Total	43.6 ± 22.0	53.5 ± 16.4	0.19[*]

[*]Comparisons performed using Student *t*-test.
[†]Comparisons performed using Mann-Whitney *U* test.

Table 3.
Comparison of physical fitness variables between patients with chronic fatigue syndrome (CFS) and healthy inactive control participants. Data presented as mean ± standard deviation. Statistically significant results are bold.

Variable	CFS (*n* = 30)	Control (*n* = 13)	*p*-Value[*]
Resting Heart Rate (bpm)	92.7 ± 13.2	97.9 ± 14.7	0.27
Peak Heart Rate (bpm)	145.1 ± 22.4	164.7 ± 7.0	**<0.001**
Peak Oxygen Uptake (mL/min/kg)	19.1 ± 4.6	27.2 ± 5.6	**<0.001**
Peak Workload (W)	114.2 ± 31.3	170.0 ± 36.2	**<0.001**
Peak Respiratory Exchange Ratio	1.07 ± 0.13	1.11 ± 0.08	0.19
Maximal Handgrip Strength (lbf)[†]	50.9 ± 13.2	58.9 ± 20.0	0.14

[*]Comparisons performed using Student *t*-test.
[†]Data of only 29 patients with CFS and 12 controls were analyzed due to data loss.
bpm = beats per minute, lbf = pound-force.

measured by the PVT and HR_p ($p < 0.05$). RER_p was associated with the Stroop no word and sleep condition reaction times ($p < 0.05$). Maximal handgrip strength was related to OSPAN accuracy error, score, and total ($p < 0.05$) but not to OSPAN math error and speed error ($p > 0.05$) (**Table 4**). No other associations between cognitive performance and physical fitness variables were observed ($p > 0.05$).

To determine whether the observed relationships in patients with CFS could not simply be interpreted as normal, we also examined the associations between the same variables in the control group. None of the significant relationships observed in the patients with CFS were found to be significant in the control group ($p > 0.05$).

Relationship Between Cognitive Performance and Physical Activity Level in Patients with Chronic Fatigue Syndrome

Only two variables measured with the SWA were significantly correlated with cognitive performance. The amount of time that patients slept per day (sleep time) was inversely related to Stroop accuracy for neutral (neutral and no word conditions) and inverse negative priming stimuli ($r = -0.47$, $r = -0.60$, and $r = -0.49$, respectively; $p < 0.05$). A negative correlation was found between the number of steps taken per day (steps) and the Stroop accuracy score for incongruent stimuli ($r = -0.53$, $p = 0.01$). The latter correlation was marginally significant in the control group ($r = -0.63$, $p = 0.05$). None of the other significant and nonsignificant relationships observed in the patients with CFS were significant in the control group ($p > 0.05$).

DISCUSSION

The present study aimed at examining the relation between cognitive performance and physical fitness in female patients with CFS. Likewise, the relation between cognitive performance and PAL was examined. In

Table 4.
Statistically significant associations between cognitive performance and physical fitness variables in patients with chronic fatigue syndrome (*n* = 26).

Variable	Peak Heart Rate		Peak Oxygen Uptake		Peak Respiratory Exchange Ratio		Maximal Handgrip Strength	
	r	***p*-Value**	***r***	***p*-Value**	***r***	***p*-Value**	***r***	***p*-Value**
Psychomotor Vigilance Task								
RT	–0.42	0.04*	–0.40	0.046*	—	—	—	—
Lapses	—	—	–0.38	0.04†	—	—	—	—
Stroop RT Conditions								
Category	–0.38	0.02†	–0.47	0.008*	—	—	—	—
Congruent	–0.41	0.02†	–0.49	0.006†	—	—	—	—
Incongruent	—	—	–0.52	0.003†	—	—	—	—
Neutral	—	—	–0.52	0.003†	—	—	—	—
No Word	–0.41	0.02†	–0.56	0.001†	–0.38	0.04†	—	—
Priming Negative Sample	–0.38	0.04†	–0.53	0.002†	—	—	—	—
Priming Negative Inverse	—	—	–0.42	0.02*	—	—	—	—
Sleep	–0.40	0.03*	–0.44	0.02*	–0.53	0.003*	—	—
Stroop Accuracy: No Word Condition	—	—	–0.38	0.04†	—	—	—	—
Operation Span Task								
Accuracy Error	—	—	—	—	—	—	–0.41	0.03*
Score	—	—	—	—	—	—	0.40	0.04*
Total	—	—	—	—	—	—	0.41	0.03*

*Associations between cognitive and physical performance variables calculated using Pearson correlation analyses.
†Associations between cognitive and physical performance variables calculated using Spearman correlation analyses.
RT = reaction time.

addition, cognitive performance and physical fitness were compared between patients with CFS and healthy controls.

Cognitive Performance

The results of the present study showed decreased choice and simple reaction time in patients with CFS relative to controls, as demonstrated by slower response times on all conditions of Stroop reaction time and the PVT, respectively. This first finding confirms previous findings also using the Stroop task as an objective measure to evaluate choice reaction times in patients with CFS [8–9]. On the PVT, we found that patients with CFS did not only demonstrate significantly longer reaction times than controls, but they also committed more errors of omission, which resulted in significantly higher lapse scores. The PVT is a test of simple reaction time that is most commonly used in sleep deprivation studies to examine the effect of this phenomenon on attention and vigilance [35–36]. In their literature review, Lim and Dinges state that sleep-deprived persons show an overall slowing of responses and an increase of lapses for lengthy periods on the PVT [36]. In the present study, we have evidence of these findings in patients with CFS as well. Consequently, Lim and Dinges adopt that sleep deprivation suppresses the ability to pay attention [36]. Perceptual, processing, or executive failures in the central nervous system are thought to increase the number of lapses in sleep-deprived persons [36]. This could be a possible explanation for the higher number of lapses determined in patients with CFS. By all means, apart from the degree of sleep deprivation, levels of exhaustion and fatigue should always be taken into account in these patients in future research.

Although we found that overall choice reaction time was lower in patients with CFS relative to controls, as evidenced by slower color naming on all conditions of the Stroop task, Stroop (semantic) interference effect in patients with CFS was not increased relative to controls. Because Stroop interference reflects selective attending ability or the ability to inhibit irrelevant information, this finding demonstrates normal semantic processing in these patients. These findings were not unexpected in that they replicate previous findings [7–9,37–38].

The reaction times of both patients with CFS and controls for the negative priming conditions (simple and inverse) compared with the incongruent condition were not significantly different (no negative priming effect). These data therefore show that both patients with CFS and controls are not capable of inhibiting distractor stimuli. To our knowledge, the present study was the first to investigate negative priming effects in patients with CFS. Surprisingly, no negative priming effect was present in controls, which may be the result of our small sample size.

We found no significant emotional interference effect (sleep-related words) in either the patients with CFS or controls. On the other hand, patients with CFS did show shorter reaction times for fatigue-related words than for neutral words. Possibly due to the high variance, this difference was not found to be statistically significant. This suggests that patients with CFS are less attentive to fatigue-related information. These findings are in line with previous reports [9,39], which did not find attentional bias toward illness-related information in individuals with CFS.

Stroop accuracy analyses showed a marginally significant lower score for the incongruent condition than the congruent condition in both groups. This could indicate that no speed-accuracy trade-off took place (patients with CFS and controls did not emphasize speed over accuracy) and consequently could demonstrate that the patients with CFS were really slower in color-naming all conditions relative to the controls. A marginally significant lower score was found in the controls for the sleep-related words condition than the category condition. Furthermore, patients with CFS were even more accurate than controls in color-naming sleep-related words. These results could suggest that sleep-related words had an emotional load on the controls but not on the patients with CFS. Interestingly, all recruited controls were related in one way or another to the patients with CFS because every patient was asked to bring a healthy and inactive relative, friend, or acquaintance to participate in the control group. Indeed, it has been previously shown that the emotional burden of CFS is felt by carers and relatives as well [40].

Regarding the OSPAN, there are two sources of data: one from the math portion of the task, which is the processing component, and one from the letter span part of the task, which is the storage component. Patients with CFS did not perform significantly worse on either one of the components, but when looking closer at the results, it is remarkable that especially the letter recall scores are worse in the patients with CFS. The reason why there is only a trend and not a significant difference in the letter span scores is the presence of the high variability between the obtained scores, which is in turn likely the result of the presence of one or more confounding variables (e.g., moment of the day the test was taken, levels of education and intelligence, menopausal state, disease duration). Thus, as evidenced several times before [6–8,11–12], it is likely that patients with CFS have a reduced working memory capacity.

Physical Fitness

Previous studies show conflicting findings in relation to physiological exercise capacity in patients with CFS [20]. Our findings suggest that female patients with CFS display a decreased exercise capacity, as evidenced by reduced VO_{2p}, reduced peak workload, and reduced HR_p. However, values of HR_{rest} and RER_p were found to be near normal. In this study, we anticipated potential sources of bias such as the lack of uniformity in sex, PAL, and utilized diagnostic criteria for CFS. All controls had an inactive lifestyle as defined by De Becker et al. [27], all participants were female, and participating patients with CFS were all diagnosed according to the 1994 CDC criteria to exclude the presence of possible psychiatric disorders.

In a previous study of patients with CFS, Van Oosterwijck et al. demonstrated that postexertional malaise, which is a term used to describe symptom exacerbation as a result of excessive exercise, is triggered by submaximal exercise and self-paced, physiologically limited exercise [41]. Consequently, it is possible to explain the reduced exercise capacity in individuals with CFS by an underlying fear of postexertional malaise. In addition, it is evidenced that patients with CFS report higher ratings of perceived exertion during exercise relative to healthy controls [42–45]. Wallman et al. therefore suggest that the reduced exercise capacity seen in some patients with CFS might be explained by an abnormal sense of effort in these individuals and/or a reluctance to push toward full capacity [45]. On the other hand, we registered a mean RER_p value of 1.07 in the patients with CFS, which demonstrates that these patients have cycled to the top of their potential. Likewise, it is well documented that patients with CFS exhibit reduced daily PALs [20–21], and (part of) the cause of this deteriorated physical exercise capacity can possibly be found in the entailed downward spiral of physical inactivity and avoidance behavior toward physical activity.

In this study, we observed no significant difference in maximal muscle (handgrip) strength between individuals with CFS and healthy controls. Although there is controversy in the literature about maximal muscle strength in patients with CFS compared with healthy controls, these results are in line with most studies that examined this parameter in patients with CFS [46–51].

Relationship Between Cognitive Performance and Physical Fitness and Cognitive Performance and Physical Activity Level

To the best of our knowledge, the present study is the first to address the association between cognitive performance and physical fitness in people with CFS. Our data showed the presence of an association between these two domains in people with CFS. Patients with reduced physiological exercise capacity were more likely to perform worse on cognitive testing. More specifically, those patients with CFS who demonstrated lower VO_{2p} and HR_p values also showed slower psychomotor speed (longer simple and choice reaction times). Furthermore, moderate correlations were found between maximal handgrip strength and letter recall (positive and negative, respectively) and accuracy errors on the math portion of the OSPAN task.

In contrast with our hypothesis, increased PALs were not associated with better cognitive performance in patients with CFS. We only observed negative relationships between sleep time, steps taken per day, and some Stroop accuracy scores. Our findings are not in line with those of Christodoulou et al. [25], who evidenced a positive relationship between cognitive impairment and functional daily activity disability, and Vercoulen et al. [24], who reported an association between low PALs and slowed motor and information processing speed in persons with CFS.

A posteriori analysis of correlations between physical exercise capacity and PALs showed a positive relationship between these domains in both groups (higher VO_{2p} values were related to higher physical activity time [>3 METs], physical activity energy expenditure [>3 METs], and mean energy expenditure). The fact that lower physical fitness but not lower PALs were associated with poorer cognitive performance, while we also found a significant positive relationship between PAL and VO_{2p}, is interesting. As a result of these findings, it can be hypothesized that PAL is a potential mediator of the relationship between VO_{2p} and cognitive function in patients with CFS.

Likewise, Wallman et al. showed an improvement in attentional function after a 12 wk graded exercise intervention [52]. This positive effect of an exercise program has already been observed in healthy people [53] and in other fatigue-related patient populations such as those with multiple sclerosis [54–55], fibromyalgia [56], Parkinson disease [57–58], and cardiac disease [59]. However, in patients with CFS there is still a paucity of objective data concerning this topic. Although weekly energy expenditure was recorded through self-report, results from the randomized controlled trial conducted by Wallman et al. showed an increase in PAL in the graded exercise group [52]. These data strengthen the hypothesis of PAL being a potential mediator of the relationship between VO_{2p} and cognitive function in patients with CFS. This is very important because there still exists an inconclusive discussion around what type of managing program is best suited for this group of patients (cognitive behavioral therapy with graded activity vs graded exercise or pacing). We therefore believe that, in order to shed more light on this discussion, future studies should explore the influence of changes in physical fitness (aerobic capacity), whether or not through changes in physical activity, on cognitive function in patients with CFS. Therefore, continued prospective research (using a randomized controlled design) is warranted.

Study Limitations

Finally, the present study has a few methodological issues that need to be mentioned. First, caution should be taken when generalizing the results to the complete CFS population, because only women were studied in order to account for bias caused by pooling of sex data. The external validity of the results is therefore limited to adult female patients with CFS who are not housebound. Second, menopausal state of the participants over 40 yr old and levels of education and intelligence were not taken into account. Third, causal interpretation of findings is precluded due to the cross-sectional nature of the study. In addition, longitudinal data are required to examine the stability of these findings in a condition such as CFS, which is characterized by high health status fluctuations over time.

On the other hand, the study also has strengths. The patient group was sufficiently powered, and we anticipated several sources of bias such as medication usage and the lack of uniformity in sex, PAL, and utilized diagnostic criteria for CFS. In addition, the measurements used are valid and represent gold standards for measuring physical fitness, cognitive performance, and PAL.

CONCLUSIONS

In conclusion, the present study confirms the presence of decreased choice and simple reaction time in people with CFS. Moreover, it evidences a significantly decreased physiological exercise capacity, but a preserved maximal handgrip strength in female patients with CFS when compared with healthy inactive controls. Lower levels of physical fitness, but not reduced PALs, were associated with poorer performance on the cognitive testing battery. These observations are important in order to design future studies exploring the influence of changes in physical fitness, whether or not through changes in physical activity, on cognitive function in patients with CFS.

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